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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,072	ROCH ET AL.	
	Examin r	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-55,86 and 137-150* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-55,86 and 137-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group IX (claims 51-55 and 86) drawn to a method for screening for drug candidates in Response to Election/Restriction (21 August 2003) is acknowledged. The traversal is on the ground(s) that search and examination of all the species as presented in the amended claims does not present a burden on the Examiner. This is found persuasive. All claims and species as currently presented will be examined. The remaining restriction requirement is still deemed proper and is therefore made FINAL.

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claims **150** and **151** been renumbered as **149** and **150**.

Status of Application, Amendments, and/or Claims

3. Claims **51-55, 86, and 137-150** are under examination.

Specification

4. The disclosure is objected to because of the following informalities: incorrect abbreviation "Ab", "BAT" [0036]; update status of application, "U.S. Patent Application No. 09/466,139, now abandoned" [0039, 0045, 0047, 0049, 0050, 0053, 0054, 0055,

0060, 0063, 0066, 0069]; misspelling "We" [0055]; missing space between characters "lymphocytes(Avraham" [0058] and "family(Bryan" [0059]; "Ab25" [0061]. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims **51-55 and 137-150** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method for screening for compounds capable of modulating the interaction of proteins or a protein complex comprising steps (a)-(d) and (i)-(iv) as set forth in claim 51 wherein the first protein is selected from the group consisting of BAT3, a fragment of BAT3 comprising amino acids 271 to 480, and a fragment of BAT3 comprising amino acids 740 to 1040 and the second protein is selected from the group comprising of glypican, a fragment of glypican comprising amino acids 400 to 483, LRP2, a fragment of LRP2 comprising amino acids 1 to 304, LRPAP1, a fragment of LRPAP1 comprising amino acids 11 to 361, transthyretin, a fragment of transthyretin comprising amino acids 7 to 148, and APP wherein said method is performed using an in vitro cellular model (such as a yeast two-hybrid system)*, does not reasonably provide enablement for *use of other fragments of said proteins, identifying drugs, or performing said method in an animal model.* The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to **use** the invention commensurate in scope with these claims.

6. The claims are drawn very broadly to methods screening for drug candidates using fragments of BAT3, glypican, LRP2, LRPAP1, transthryretin, and APP and fragments thereof. The claim language encompasses all fragments of said proteins, from a single amino acid to the full-length protein minus a single atom. Further the language of said claims encompasses both *in vivo* and *in vitro* assays as well as nonhuman and human subjects in which to practice the invention.

7. The specification teaches screening for drug candidates capable of modulating the interaction of proteins or a protein complex comprising steps (a)-(d) and (i)-(iv) as set forth in claim 51 wherein the first protein is selected from the group consisting of BAT3, a fragment of BAT3 consisting of amino acids 271 to 480, and a fragment of BAT3 consisting of amino acids 740 to 1040 and the second protein is selected from the group consisting of glypican, a fragment of glypican consisting of amino acids 400 to 483, LRP2, a fragment of LRP2 consisting of amino acids 1 to 304, LRPAP1, a fragment of LRPAP1 consisting of amino acids 11 to 361, transthyretin, a fragment of transthyretin consisting of amino acids 7 to 148, and APP. The Specification teaches performing said method *in vitro* cellular model (yeast two-hybrid system).

8. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using as of yet undisclosed and ill-defined fragments of BAT3, glypican, LRP2, LRPAP1, transthyretin, and APP. The specification fails to provide any guidance for the successful use of any of the undisclosed fragments, and since resolution of the various complications in regards to

predicting the activity or binding specificity of polypeptide fragments is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulation and synthesis or isolation of fragments of BAT3, glypican, LRP2, LRPAP1, transthyretin, and APP and then to practice the invention with all the applicable combinations. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

9. Additionally, a person skilled in the art would recognize that predicting the efficacy of using undisclosed and poorly defined polypeptide fragments solely on the performance of a single fragment or the full-length polypeptide as highly problematic {see MPEP §2163 [R-1](a)}. Thus, although the specification prophetically considers and discloses general methodologies of using fragments of BAT3, glypican, LRP2, LRPAP1, transthyretin, and APP, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) **The breadth of the claims;**
(B) **The nature of the invention;**
(C) **The state of the prior art;**
(D) **The level of one of ordinary skill;**
(E) **The level of predictability in the art;**
(F) **The amount of direction provided by the inventor;**
(G) **The existence of working examples; and**
(H) **The quantity of experimentation needed to make or use the invention based on the content of the disclosure.**

10. The following references are cited herein to illustrate the state of the art of protein biochemistry.

11. Concerning the breadth of the claims, Rosen *et al.* (August 1993) "Thyroxine Interactions with Transthyretin: A Comparison of 10 Different Naturally Occurring Human Transthyretin Variants." Journal of Clinical Endocrinology and Metabolism **77**(2): 370-374 teaches that point mutations in transthyretin (TTR) affect their binding specificity (Figures 1-4). Therefore the claims as written comprise an invitation to experiment for the skilled artisan to determine which TTR fragments bind BAT3 through trial and error.

12. On the nature of the invention, the term "drugs" contains an implicit meaning of use for therapy whereas the term "compounds" is a less specific term which may contain "drugs" within the rubric thereof but is does not specifically require any given compound to possess a property outside that which is identified via practicing the claimed method (see MPEP §2111). Since the term "drugs" has this implicit meaning and the skilled artisan is not apprised of the potential or actual therapeutic value of any given compound identified by practicing the invention, said method does not enable one skilled in the art to practice it for the purpose of identifying potential therapeutics. The method as claimed is only enabled in so far as "compounds" which "modulate the interaction" of two given proteins or protein complexes may be identified and is not enabling for the identification of therapeutics, i.e. "drugs". While certain "compounds" may indeed be of therapeutic value, this outside the scope of the method as set forth by the instant Specification and requires further experimentation in the absence of any guidance.

13. On the nature of the invention, Multhaup *et al.* (28 November 1994) "Interaction between the zinc(II) and the heparin binding site of the Alzheimer's disease βA4 amyloid precursor protein (APP)." FEBS Lett. **355**(2): 151-154 teaches that APP exists in at least eight distinct isoforms: L-APP_{677}, APP_{695}, L-APP_{696}, APP_{714}, L-APP_{733}, APP_{751}, L-APP_{752}, and APP_{770}. Therefore the claims as written comprise an invitation to experiment for the skilled artisan to determine which APP fragments bind BAT3 through trial and error.

14. Finally, regarding fragments of BAT3, glypican, LRP2, LRPAP1, transthyretin, and APP polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of

sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the

claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic consideration of BAT3, glypican, LRP2, LRPAP1, transthyretin, and APP fragments to the full-length proteins or defined fragments demonstrated in the Specification as exemplified in the references herein.

16. Claim **86** is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how is the complex detected.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claim **86** is rejected under 35 U.S.C. 102(b) as being anticipated by Williamson *et al.* (6 December 1996) "Secreted Glypican Binds to the Amyloid Precursor Protein of Alzheimer's Disease (APP) and Inhibits APP-induced Neurite Outgrowth." The Journal of Biological Chemistry **271**(49): 31215-31221 (**IDS B#46**). Williamson *et al.* teaches a method comprising an APP affinity chromatography column over which conditioned media was poured to determine if any components therein bound said APP thus meeting the limitations of claim 86 (pp. 31216; Figure 1).

19. Claim **86** is rejected under 35 U.S.C. 102(b) as being anticipated by Smeland *et al.* (1997) "Binding of perlecan to transthyretin *in vitro*." Biochem. J. **326**: 829-836. Smeland *et al.* teaches a method comprising a transthyretin affinity chromatography column over which conditioned media was poured to determine if any components therein bound said transthyretin thus meeting the limitations of claim 86 (pp. 829-830; Figures 1-2).

20. Claim **86** is rejected under 35 U.S.C. 102(e) as being anticipated by WO 02/23193 A1 (21 March 2002). WO 02/23193 teaches a method comprising contacting glypican with a test compound and then determining if said compound has bound to said glypican thus meeting the limitations of claim 86 (pp. 7, 10, 19, and 22; Figure 3; claims 1-6).

Summary

21. Claims **51-55, 86, and 137-150** are hereby rejected.

22. The following articles, patents, and published patent applications were found by the Examiner during the art search are not relied upon but are considered pertinent to applicant's disclosure:

a. US 2002/0098511 A1 (25 June 2002) Heichman *et al.*

b. US 2003/0103980 A1 (5 June 2003) Korc & Lander

c. WO 00/23109 (27 April 2000) Lander & Korc

d. Lans *et al.* (4 April 1994) "Different competition of thyroxine binding to transthyretin and thyroxine-binding globulin by hydroxy-PCBs, PCDDs, and PCDFs." European Journal of Pharmacology **270**(2-3): 129-136

e. Golabek *et al.* (19 May 1995) "Amyloid β binding proteins in vitro and in normal human cerebrospinal fluid." Neuroscience Letters **191**(1-2): 79-82

f. Wang & Liew (1994) "The human BAT3 ortholog in rodents is predominantly and developmentally expressed *in testis*." Molecular and Cellular Biochemistry **136**: 49-57

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
October 6, 2003